Spinal Cord Glioma

Timothy Malouff, MD
Faculty: Jennifer Peterson, MD
Mayo Clinic Florida
Jacksonville, FL
Case

• 22 year old female with no relevant PMH presented with a one month history of mid-back pain and a small area of numbness on her knee.
• ROS: Positive for gradually progressive bilateral lower extremity weakness and paresthesia.
  – No bladder or bowel dysfunction.
  – No saddle anesthesia
Case

• SH: No previous surgeries
• FH: No family history of cancer or neurologic disorders.
• SH: Nonsmoker, no alcohol use, no drug use
• Medications: None
• Exam: 3/5 strength in the bilateral lower extremities, otherwise unremarkable
Case

• Given her continued progressive symptoms despite conservative treatment with physical therapy, an MRI was obtained
Case

• MR of the thoracic spine
  – T11-T12 centrally located intramedullary expanding lesion with well defined borders and mild heterogeneous enhancement
  – Radiographically consistent with ependymoma

• MR of the brain, cervical spine, and lumbar spine were negative
T2 imaging: Centrally located mass with well defined borders

Most consistent with ependymoma
Workup (NCCN v3.2019)

• Spine MRI (cervical, thoracic, and lumbar)
• CT myelogram if MRI is contraindicated
Treatment options (per NCCN)

Intramedullary tumors

- Well defined/circumscribed on MRI
  - Asymptomatic: Observation
  - Symptomatic: Maximum safe resection

- Poorly defined on MRI
  - Asymptomatic: Observation
  - Biopsy
  - Symptomatic: Biopsy
Case

• She underwent T11-T12 laminectomy and intramedullary spinal cord tumor resection
  – Postoperative course was uncomplicated
  – Per surgeon: 60% removed

• Pathology: Diffuse midline glioma (WHO grade IV)
  – H3K27-M mutant
  – ATRX retained, IDH-1 negative, high Ki67
  – MGMT not performed
Postoperative MRI

- 1 month post-op
- Significant decrease in size of abnormality, although enhancement remains
- Suggesting subtotal resection
Adjuvant Treatment

• Multidisciplinary approach
• Clinical trials if available
• Temozolomide with radiation therapy (as per glioblastoma)
  – Pregnancy test!
  – Fertility counseling
    • Please see manuscript by Ghadjar et al for an excellent review on fertility preservation
      (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4341866/pdf/13014_2015_Article_353.pdf)
Adjuvant Radiation

- VMAT using 6MV photons
- 45 Gy in 25 fractions to low risk PTV followed by a 9 Gy boost to residual disease
- GTV: Gross tumor
  - CTV_45: GTV + 1.5 cm sup/inf expansion
  - PTV_45: CTV + 1 cm
- PTV_54: GTV +1 cm (CBCT used)
- Consider contouring ovaries (out of field in this patient)
- Minimize hot spot
  - Cord received a point dose of <56 Gy
Follow up

• She tolerated treatment well without significant toxicity

• She was started on Depakote by neuro-oncology given possible benefit in H3K27M gliomas (see Literature Review)

• She is continuing adjuvant temozolomide and tolerating well 1 month after radiation
SPINAL CORD GLIOMAS
Spinal Cord Gliomas

- Spinal cord malignancies account for 2-4% of all primary CNS cancers
  - High grade spinal cord gliomas account for 0.2% of all glioblastomas
- Typically treated similar to a GBM
  - Maximum total resection followed by adjuvant chemotherapy and radiation
  - Typically treated to 54 Gy (may treat to 60 Gy depending on disease site and institution)
  - Test for H3K27M when clinically indicated
    - Improved prognostic information, possible benefit with HDAC-inhibitors
- Local failures are most common
  - Most occur in-field within 2 years
- Most common cause of death: Sequelae from paraplegia (infection, etc)
Clinical Pearls

• Spinal cord ends at L1-2 in adults
  – L3-4 in children

• 2/3 of spinal cord tumors are extramedullary
  – 1/3 intramedullary

• 90% are low grade (ependymomas)
  – Most commonly in lumbar/sacral spine
  – Present as well defined regions of enhancement, typically more central and symmetric

• Astrocytomas are most common in cervical or thoracic spine
  – Present as asymmetric expansion on MRI
Toxicities

• Radiation induced myelopathy presents as paresthesia, weakness, pain/temperature loss, or bladder and bowel dysfunction
  – 12-29 months after RT

• Risk of myelopathy (QUANTEC)
  – 54 Gy: <1%
  – 61 Gy: <10%
  – 13 Gy in 1 fraction (SRS): <1%
  – Cervical spine is less sensitive than thoracic spine (consider dose escalating to 60 Gy)
LITERATURE REVIEW
Retrospective review of 183 patients treated with surgery vs surgery and PORT for spinal cord gliomas

Included low, intermediate, and high grade tumors
Abdel-Wahab et al

• For astrocytoma
  – PFS was 42% at 5 years, 29% at 10 years, and 15% at 15 years
  – OS was 59% at 5 years, 53% at 10 years, and 32% at 15 years

• Of note, RT group had few complete resections when compared to surgery alone
Conclusion: PORT reduced progression in low and moderate grade astrocytomas.
• Single institution analysis of 6 patients with high grade spinal cord gliomas

• All patients underwent subtotal resection
  – 3 received postoperative radiation (54 Gy in 30 fractions)
  – 3 received postoperative chemo (temozolomide and bevacizumab)
Yanamadala et al

• At 3 month follow-up
  – KPS was stable in 50% of patients
  – All patients had decreased KPS at 1 year
• 100% overall survival at 1 year
Conclusions from Yanamadala et al

There is an excellent 1 year survival, although with a decline in functional status, for patients with high grade spinal cord gliomas treated with subtotal resection +/- adjuvant chemoRT
Role of H3K27M?

• H3K27M: Substitution of lysine for methionine at position 27 in histone 3
  – Mutation in one of several H3 genes, including \textit{H3F3A} or \textit{HIST1H3B/C}
  – Almost always midline if present
  – Some evidence of improved outcomes with HDAC inhibitors (sodium valproate) in H3K27M tumors
    • Remains controversial
    • Largely based on pre-clinical studies and case reports
• Karremann et al published a study suggesting H3K27M as a poor prognostic factor for high grade gliomas in all regions of the CNS
Meta-analysis of 6 studies and 474 patients

The presence of the mutation was associated with worse prognosis (HR 3.630) and a worse overall survival (by 2.3 years)
• Sodium valproate causes dose-dependent decrease in DIPG cell line viability

• Valproate causes increase in acetylation of histone H3, reducing cell viability by induction of apoptosis

• Potentiates carboplatin

• **Conclusion:** Based on pre-clinical work, valproate may be used as an adjuvant treatment in DIPG
Case report of a 39 year old with cervical intramedullary H3K27M-mutated diffuse midline glioma

- Underwent subtotal resection
- Treated with 54 Gy and concurrent and adjuvant temozolomide
- Started on valproic acid at time of disease progression (25 months after diagnosis)
- Passed away at 31 months after diagnosis
Summary

• High grade spinal cord gliomas are rare
• H3K27M is a poor prognostic factor
• Treatment consists of biopsy/resection followed by radiation (54 Gy in 30 fx) and chemo (similar to GBM)
• Try to keep the spinal cord dose <54 Gy for <1% risk of myelopathy
• Most relapses occur in-field
References


Please provide feedback regarding this case or other ARRO cases to arrocase@gmail.com